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EDITORIAL

The current status of percutaneous mitral valve repair

Valvular heart disease is a common clinical problem and mitral valve regurgitation is the lesion seen most frequently. The mitral valve is a complex structure and regurgitation of the valve may occur due to abnormalities of the valve leaflets, the chordae tendineae, the papillary muscles or the mitral valve annulus. The aetiology of mitral regurgitation may be classified as either organic or functional. Organic regurgitation is due to structural changes in the valve or subvalvar apparatus, such as degenerative (including mitral valve prolapse) and rheumatic disease, infective endocarditis and annular calcification. Functional regurgitation occurs in the setting of a structurally normal valve when changes in left ventricular geometry lead to failure of coaptation of the valve leaflets. This may be secondary to underlying coronary artery disease or a dilated cardiomyopathy.

Organic mitral regurgitation occurs when degenerative conditions lead to structural changes in the leaflets or the subvalvar apparatus. Mitral valve prolapse occurs when part (or all) of one (or both) of the valve leaflets displace retrogradely into the left atrium during systole. In developed countries, this is the most common cause of chronic mitral regurgitation. Several causative genetic chromosomal abnormalities have been identified although the disease may also be acquired. A defect in collagen results in the valve leaflets and chordae tendineae becoming baggy and fragile. As a result, when the valve closes, the leaflets are not pulled taught and prolapse into the left atrium. The chordae are prone to rupture and over time there is annular dilatation. Although many patients remain asymptomatic and have a normal life expectancy, between 5% and 10% of patients may progress to severe mitral regurgitation (Barlow and Pocock, 1979). Patients who develop symptoms or have signs of significant mitral regurgitation with left ventricular dilatation and/or dysfunction should be considered for surgery.

The current surgical options are mitral valve replacement with a mechanical or biological prosthesis or repair of the patient's native valve. Although there are no randomised trials comparing mitral valve replacement and repair, a meta-analysis of the observational studies favoured mitral repair in survival outcomes (Shuhaiber and Anderson, 2007). The most common lesion identified is prolapse of the middle scallop of the posterior leaflet. Repairs of the anterior leaflet or both leaflets are more complicated. The goals of surgical repair are to ensure an adequate surface of coaptation of both leaflets in systole, restore full leaflet motion and prevent progressive annular dilatation by inserting an annuloplasty ring. The operative mortality is typically up to 3% (Gillinov et al., 1998) and recurrence of the mitral regurgitation may occur in up to 30% of patients (Filsoufi and Carpentier, 2007).

Mitral regurgitation may result from rheumatic heart disease, although mitral stenosis or mixed mitral valve disease occur more commonly. Ischaemic mitral regurgitation results from the sequelae of underlying coronary artery disease. Acute myocardial ischaemia may result in transient dysfunction of the subvalvar apparatus and myocardial infarction may cause permanent dysfunction of the subvalvar apparatus. Generally the outcome of patients with ischaemic mitral regurgitation is worse than those patients with similarly severe regurgitation from another cause, due to the superimposed left ventricular dysfunction. In patients with acute papillary muscle rupture, urgent mitral valve surgery with revascularisation should be considered. The case for surgery with chronic ischaemic mitral regurgitation is less clear cut. Mitral valve replacement and/or mitral valve annuloplasty with concomitant coronary artery grafting needs to be considered.

With functional mitral regurgitation, there is incomplete mitral valve closure in the setting of a structurally normal valve. This may occur due to global left ventricular dysfunction reducing the ventricular force acting to close the leaflets, dilatation of the mitral annulus and alterations in left ventricular geometry at the site from which the papillary muscles arise. Although all three factors may contribute to the mitral regurgitation it appears that the predominant mechanism is apical displacement of the papillary muscles with tenting of the leaflets away from the annulus and subsequent incomplete leaflet coaptation (Levine and Schwammenthal, 2005).

Functional mitral regurgitation is found frequently in patients with impaired left ventricular systolic function and is associated with a worse prognosis in this group of patients. Furthermore, there is an incremental risk of mortality with

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increasing grades of mitral regurgitation. In a 10 year cohort study, the prevalence and prognostic implication of mitral regurgitation was evaluated in patients undergoing echocardiography within 30 days of myocardial infarction. Mitral regurgitation was found in 50% of patients. After around 5 years of follow up, mitral regurgitation was associated with a greater than threefold risk of heart failure and the presence of moderate/severe regurgitation was independently associated with a 55% increased risk of death (Bursi et al., 2005).

Medical therapy may reduce regurgitant volumes in patients with functional mitral regurgitation, but the primary effect is for treatment of the antecedent heart failure. Beta-blockers and ACE inhibitors usually help to restore the normal orientation of the papillary muscles to the annulus. Vasodilators, including nitrates and hydralazine, in association with diuretics may reduce the severity of mitral regurgitation. A subset of patients with an increased QRS duration may be suitable for cardiac resynchronisation therapy (Auricchio and Abraham, 2004). The standard surgical treatment for functional mitral regurgitation involves annuloplasty with a ring that is designed to correct annular dilatation, restore leaflet coaptation and reduce the effective regurgitant orifice area. Chronic volume overload contributes to progressive ventricular remodelling, which in term begets progressive mitral regurgitation. Surgical correction may break this cycle, although the operative risk in this patient population is not insignificant. When the various observational studies are examined, it becomes apparent that the operative risk is between 3% and 6% (Wu et al., 2005; Mihaljevic et al., 2007). In most patients there is an improvement in NYHA functional class, exercise capacity and quality of life (Mihaljevic et al., 2007; Acker et al., 2006). Some, but not all, studies have demonstrated positive functional outcomes, such as reverse remodelling and reductions in end-diastolic and end-systolic volumes (Acker et al., 2006; Bolling et al., 1998). There are therefore reservations regarding surgery for functional mitral regurgitation in view of the high surgical mortality, the fact that the primary problem is with advanced left ventricular dysfunction and the high rate of recurrence of valvular regurgitation following surgery. It is clear that careful patient selection is vital since currently there are no randomised controlled trials comparing surgery with medical or device therapy.

Percutaneous treatment of the mitral valve has been in development since balloon valvuloplasty for mitral stenosis was performed over 25 years ago (Inoue et al., 1984). The therapies for mitral regurgitation have been more difficult to refine. Currently we have various options available which follow similar approaches to the established surgical procedures. These include leaflet repair, coronary sinus annuloplasty, direct annuloplasty as well as chamber remodelling devices. Although mitral valve replacement and valve repair are well established and effective methods of treating mitral regurgitation, some patients may not be suitable for surgery. The presence of major co-morbidity or severe left ventricular dysfunction may be associated with a high surgical risk. The percutaneous technologies negate the use of sternotomy and cardiopulmonary bypass and may offer an alternative approach in high risk patients.

It is possible to create a double orifice within the mitral valve by suturing the free edges of the anterior and posterior leaflets together using a percutaneous approach. This technique was first described by Alfieri in 1990. It may be useful in patients with mitral regurgitation resulting from central malcoaptation of the valve. When this technique is used during open heart surgery it is common practice to deploy an annuloplasty ring simultaneous. This is not performed in the percutaneous procedure and the added benefit of an annuloplasty ring remains uncertain. The Mobius device uses a transeptal suction catheter to secure the mitral valve leaflets and subsequently deploy percutaneous sutures. Feasibility trials in animals and humans proved unsatisfactory and currently this technique is not being used in clinical practice. The Mitraclip device uses a transeptal catheter with a metallic clip to grasp the two free edges of the anterior and posterior leaflets and join them. Transoesophageal echocardiography guides the deployment and is used to assess the valve throughout the procedure. Clips can be removed if not satisfactory without injury to the leaflets or subvalvar structure. The operator can optimise the reduction in mitral regurgitation by trialing several points along the line of coaptation. The transoesophageal echocardiogram enables functional assessment of the valve and the degree of regurgitation during the procedure. If the operator is unable to deploy the Mitraclip device with a satisfactory result, the device can be removed entirely and other options considered. The design of the device does not preclude subsequent surgical intervention even if left in situ. It is possible to deploy an additional Mitraclip if necessary.

The phase I feasibility trial of Mitraclip, EVEREST I, included patients with functional or degenerative mitral regurgitation of grade 3 or above. Patients with rheumatic mitral regurgitation and severe left ventricular dysfunction were excluded. The Mitraclip was implanted in 42 patients and in 74% the degree of mitral regurgitation was reduced to grade 2 or below at the time of discharge. This improvement was maintained on echocardiographic follow up at 6 months (Herrmann and Feldman, 2006). The first randomised trial comparing Mitraclip with conventional surgery in patients with at least grade 3 regurgitation, EVEREST II, excluded patients with left ventricular dysfunction and/or annular dilatation. The early results have demonstrated a reduction in mitral regurgitation to grade 1 or less in 64% of patients. This was associated with clinical improvement and a reduction in NYHA class. At 3 years there was freedom from death of 90% and freedom from surgery of 76% in those undergoing percutaneous repair (Feldman et al., 2009). The percutaneous procedure has been associated with a low morbidity and mortality. Partial clip detachment occurred in 9% of cases – i.e. detachment from one of the two valve leaflets. The vast majority of patients reported had mitral valve prolapse. It remains to be seen whether this technique will have the same success in patients with functional mitral regurgitation.

The EVEREST II high risk registry recruited 78 symptomatic patients with mitral regurgitation of grade 3 or more who were considered to be at high risk from conventional surgery (Kar, 2009). Their surgical mortality was considered to be greater than 12% and most had several co-morbidities. Forty six patients had functional mitral regurgitation and 32 had organic regurgitation. The acute procedural success was 96%. The mean predicted 30 day mortality was 17.8%, with an actual mortality of 7.7%. At 12 months, 74% of patients were NYHA functional class I or II as compared with 9% prior to the procedure. There was an associated improvement in left ventricular volumes and function.

A variety of devices have been developed to modify the mitral valve annulus indirectly via the coronary sinus, including the MONARC device, the CARILLON device and the PTMA device. The MONARC device consists of two self expanding nitinol anchors connected by a bridge which gradually shortens following implantation. This has the effect of anterior displacement of the posterior mitral annulus with reductions in mitral annulus diameter and septal lateral distance. The EVOLUTION I trial evaluated the safety and efficacy of the device in 72 patients with functional mitral regurgitation due to either dilated or ischaemic cardiomyopathy (Harnek, 2009). Successful implantation occurred in 82% of patients. At 2 year follow up, 55% of patients had at least one grade reduction in the degree of mitral regurgitation. There were more responders if the degree of regurgitation was greater at baseline. Of these with grade 3 or more regurgitation at baseline, 80% had an improvement of at least 1 grade at follow up. The early data indicates feasibility, safety and durability of the MONARC device, with larger trials ongoing (EVOLUTION II).

The CARRILON device consists of distal and proximal nitinol based anchors that are separated by a metal bridge. After the distal anchor is deployed in the great cardiac vein, manual tension is applied to the system which results in plication of the mitral annulus. As there is an immediate shortening of the coronary sinus, deployment of the device can be guided by echocardiographic measures of the reduction in mitral regurgitation. Unlike the MONARC system, the CARILLON device is fully retrievable up to final release. This may be helpful if there is concern regarding coronary artery compression, displacement of the distal anchor or insufficient reduction in mitral regurgitation.

The AMADEUS trial evaluated the feasibility and safety of the CARILLON device in 48 patients with either dilated or ischaemic cardiomyopathy and moderate/severe mitral regurgitation. A total of 18 patients did not have the device implanted due to problems with access, coronary artery compromise or inadequate reduction in mitral regurgitation. At 6 month follow up there was a reduction in the degree of mitral regurgitation and an improvement in symptoms. At baseline 80% of patients were in NYHA class III or IV whereas at 6 months 88% were in NYHA class I or II (Schofer et al., 2009). A second study, the TITAN trial, is ongoing and will evaluate the longer term safety and efficacy (up to 5 years).

The PTMA device consists of a polytetrafluoroethylene (PTFE) catheter that is delivered into the coronary sinus via the subclavian vein, with the distal tip seated in the anterior interventricular vein, and the proximal hub left in a subclavian pocket to enable further access at a later date. The catheter contains three separate lumens through which nitinol rods of varying stiffness, length and taper can be inserted. The device produces an outward force at its proximal and distal segments such that the mid-portion of the posterior mitral annulus is displaced anteriorly with subsequent reduction of the septal–lateral dimension and mitral regurgitant orifice. Since the number, stiffness and length of the rods can be varied with time, modification of the geometry of the mitral annulus can be achieved. The PTOLEMY I trial evaluated the feasibility and safety of the PTMA device in 27 symptomatic patients with moderate-severe functional mitral regurgitation. The device was successfully implanted in only 9 patients. In these patients, there was a reduction in the degree of mitral regurgitation and a reduction in the mitral annulus septal–lateral dimension (Sack et al., 2009).

Direct mitral valve annuloplasty has been performed using the Mitralign system. A guiding catheter is delivered to the left ventricle using a retrograde transaortic approach and positioned beneath the posterior mitral leaflet. Radio frequency is used to penetrate a number of wires through the posterior annulus which are then anchored. The anchors are connected by a drawstring suture which can reduce the annular dimensions when tethered (Alqoofi and Feldman, 2009). At the present time, little clinical data is available.

In conclusion, it is now possible to treat both organic and functional mitral regurgitation using a percutaneous approach. These devices are predominantly designed to either enable direct repair of the mitral leaflets or to achieve mitral annuloplasty via a coronary sinus approach. The early studies of feasibility, safety and clinical response have been encouraging. It is likely that these devices will be used increasingly in future years and further developments/modifications will continue to be made. As further clinical trials are conducted it will become clearer as to which patients will benefit from which device and also at what stage the devices should be used during the natural history of the patients mitral valve regurgitation.

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